Review

Biological Psychiatry

Translating the Habenula—From Rodents to Humans

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ABSTRACT

The habenula (Hb) is a central structure connecting forebrain to midbrain regions. This microstructure regulates monoaminergic systems, notably dopamine and serotonin, and integrates cognitive with emotional and sensory processing. Early preclinical data have described Hb as a brain nucleus activated in anticipation of aversive outcomes. Evidence has now accumulated to show that the Hb encodes both rewarding and aversive aspects of external stimuli, thus driving motivated behaviors and decision making. Human Hb research is still nascent but develops rapidly, alongside with the growth of neuroimaging and deep brain stimulation techniques. Not surprisingly, Hb dysfunction has been associated with psychiatric disorders, and studies in patients have established evidence for Hb involvement in major depression, addiction, and schizophrenia, as well as in pain and analgesia. Here, we summarize current knowledge from animal research and overview the existing human literature on anatomy and function of the Hb. We also discuss challenges and future directions in targeting this small brain structure in both rodents and humans. By combining animal data and human experimental studies, this review addresses the translational potential of preclinical Hb research.

Keywords: Addiction, Depression, Habenula, Human, Reward, Rodent

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The habenula (Hb) is a bilateral epithalamic structure, evolutionary conserved among vertebrates (1–3). This small brain nucleus is composed of two subdivisions—the medial (MHb) and the lateral Hb (LHb)—and has a central anatomic position in the brain, connecting the forebrain to the ventral midbrain and hindbrain (4,5). The Hb regulates midbrain monoaminergic systems, notably dopamine and serotonin, and integrates cognitive with emotional and sensory processing.

A key study in rhesus monkeys originally described the structure as a brain nucleus that is activated in anticipation of aversive outcomes, or failure to obtain reward, and in turn suppresses motor behavior (6). Hb function has since attracted increasing attention in both neuroscience and the clinic. Preclinical data have now accumulated to show that Hb encodes both rewarding and aversive aspects of external stimuli. The general view from animal research is that Hb activity prevents behaviors leading to negative reward such as punishment, while reinforcing behaviors with positive reward value (7), thus driving motivated behaviors and decision making (8). Consequent to this highly integrative function, Hb also contributes to learning and memory (9) and to a range of other behaviors (8,10). Not surprisingly, therefore, Hb dysfunction has been associated with psychiatric disorders, and studies in patients have established evidence for Hb involvement in major depression (11,12), addiction (11,13), and schizophrenia (14), as well as in pain and analgesia (10).

Although still limited, human Hb research is expected to develop rapidly in the next decade, and knowledge on Hb anatomy, connectivity, and function in nonhuman primates and rodents is increasing exponentially (15). Here, we briefly summarize current knowledge from animal research and extensively review the existing human literature on Hb structure and function. Focus is on psychiatric disorders, and a section on pain and analgesia is also proposed (Supplement). We also discuss the translational potential of preclinical research to understand Hb function in humans and for psychiatry.

ANATOMY

Rodents

Most knowledge on Hb connectivity, as well as structural characteristics and neurochemistry of Hb neurons, stems from studies in animals. In brief, retrograde and anterograde tracing studies in rodents (4,16) and electrophysiological studies in nonhuman primates (5) have provided a detailed description of afferent and efferent connections of the Hb complex, summarized in Figure 1. Because of their distinct input/output structures, the LHb and MHb seem to form parallel channels, regulating the information flow from forebrain to midbrain.

Electrophysiological and morphologic analyses of rat Hb slices show distinct intrinsic circuitries within the two nuclei, confirming different information processing at the two sites, and also reveals asymmetrical MHb projections to the LHb within the Hb complex (17). The latter observation, which deserves further investigation, suggests potential interactions

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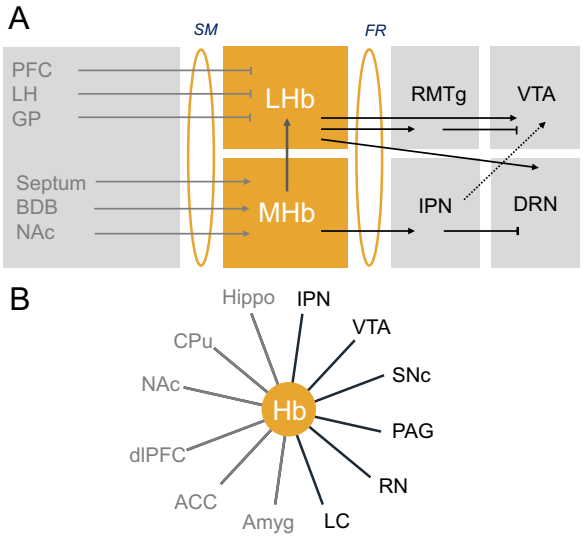

Figure 1. Habenula (Hb) connectivity in rodents and humans. Key pathways connecting medial Hb (MHb) and lateral Hb (LHb), the two subdivisions of the Hb, to other brain structures. Hb connectivity is embedded in brain circuits classically described as reward and emotion circuits, whose dysfunction is associated to psychiatric diseases reviewed here. **(A)** Structural connectivity in animal studies. The LHb receives inhibitory inputs from the prefrontal cortex (PFC), ventral pallidum, globus pallidus (GP), and lateral hypothalamus (LH) through the stria medullaris (SM) and, in turn, sends information to monoaminergic nuclei (5). Projections of LHb to dopaminergic neurons have been best described and include direct [ventral tegmental area (VTA) (99)] and indirect [tail VTA (100,101)] projections. A recent tracing study further revealed an equal number of LHb projections to either dopaminergic (VTA) or serotonergic [dorsal raphe nucleus (DRN) and median raphe nucleus (MnR)] nuclei, which are mostly but not exclusively segregated, indicating that LHb regulates the two monoamine nuclei either independently (most LHb projecting neurons) or jointly (few heterogeneously distributed LHb projecting neurons) (102); both projections are excitatory (11,103). The MHb circuitry is less well known. The medial nucleus receives mainly excitatory inputs from the septum, nucleus accumbens (NAc), and broca diagonal band (BDB) (4,5) and has excitatory projections to the rostromedial tegmental nucleus (RMTg) but mainly and massively to the interpeduncular nucleus (IPN), which in turn projects to the VTA and possibly the raphe nuclei (103). Thus, both MHb and LHb regulate in turn the VTA, DRN, and possibly other midbrain and hindbrain structures such as the locus coereulus (LC) (102). Asymmetrical projections from MHb to LHb have been described (17). **(B)** Functional connectivity in human studies. Hb connectivity is established for both forebrain (in gray) and midbrain/hindbrain (in black) structures by functional magnetic resonance imaging (10,20,104). ACC, anterior cingulate cortex; Amy, amygdala; CPu, caudate putamen; dlPFC, dorsolateral prefrontal cortex; FR, fasciculus retroflexus; Hippo, hippocampus; PAG, periaqueductal gray; RN, raphe nucleus; SNC, substantia nigra compacta.

across the two circuitries whose functional implications remain unknown. Whether similar parallel and potentially interacting LHb/MHb networks operate in humans is unknown.

The analysis of LHb cytoarchitecture in rat brain slices shows high morphologic heterogeneity, which is unrelated to electrophysiological characteristics of the neurons (18). The latter appear surprisingly homogenous throughout the LHb nucleus and include neuron populations with silent, tonic, or bursting spontaneous activities, as well as neuroglialform cells that could be interneurons (18). MHb cells are classified into only two types based on their dendritic structural characteristics, and, regardless of their anatomy, all show similar electrophysiological activity (17). Notably, the latter study also shows the existence of asymmetrical projections from MHb to LHb only (17).

Immunostaining, in situ hybridization, and anterograde tracing experiments show that LHb neurons are mostly glutamatergic, with some gamma-aminobutyric acidergic (GABAergic) neurons (16). LHb neurons are also characterized by heterogeneous expression of monoaminergic receptors across subnuclei, mainly dopaminergic D_2 receptors and serotonin 5-HT_{2C} receptors (16). Similarly, MHb contains mainly glutamatergic neurons distributed into three phenotypically distinct populations, that is, neurons expressing glutamate alone or coexpressing either substance P or acetylcholine (16,19).

Humans

Anatomic description of Hb in the human brain remains limited. As for the rodent Hb, the human Hb is also located next to the third ventricle above the thalamus and is approximately 5–9 mm in diameter with a total volume in the range of 30–36 mm^3 (20) [mouse Hb is 0.8 mm in height and width for comparison (21)]. Histologic examination of postmortem human brain shows partition of Hb into medial and lateral parts, connected by the Hb commissure, similarly to the partition observed in rodents (22). Another morphologic and immunohistochemical analysis showed that overall, the MHb subnuclear organization in humans is similar to that observed in rodents, whereas the shape, relative size, and intranuclear organization of the LHb show significant difference (23). One important difference resides in the substantially enlarged dorsal part of the human LHb that shows that $GABA_B$ receptors are immunoreactive cells. This growth in size possibly indicates increased influence of limbic and striatal afferents into the LHb of humans compared with rodents (23).

Apart from these postmortem studies and owing to its particularly small size, the human Hb was difficult to investigate structurally until recently. Ultra-high-resolution magnetic resonance imaging (hr-MRI) at 7T now allows researchers to visualize and explore the structure noninvasively.

With the use of 7T hr-MRI, Strotmann *et al.* (24) were able to discriminate MHb, LHb, and the habenular commissure in vivo and also explored the structural connectivity of the Hb. Tractographic analysis of diffusion-weighted MRI data revealed fiber tracts connecting Hb to other brain regions for both MHb (anterior posterior direction, in the form of the retroflexus fasciculus identified in rodents) and LHb (anterior posterior direction and superior inferior direction) (24). The general topography of Hb connecting forebrain and mid/hindbrain, therefore, appears similar in rodents and humans. In another study these researchers used 7T ultra hr-MRI ex vivo to further differentiate subnuclei within the Hb. High-resolution T1- and T2-weighted images with 300- and 60-μm isotropic resolution, respectively, revealed LHb heterogeneity with two distinct lateral and medial substructures (25). Ideally, these ex vivo results should help in interpreting in vivo structural MRI data (24,25).